PATENT
CASE PHAR-1550

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 6, 031,007

Granted February 29, 2000

Patentees Arne Brodin, Raymond Fynes, Lars Heijl, Adela Nyqvist-Mayer, Marie Scherlund

Assignee Maillefer Instruments Trading S.a.r.l.

FOR NEW PHARMACEUTICAL COMPOSITION WITH ANESTHETIC EFFECT

Date February 13, 2004

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Mail Stop Patent Extensions
Ms. Karin Forriter, Esq.
Crystal Plaza Three, D09
Arlington, VA 22202

Request for Extension of Patent Term Pursuant 35 U.S.C. § 156

Sir

Applicant Maillefer Instruments Trading S.a.r.l. of Ballaigues, Switzerland (MITS), the owner of record of US 6,031,007, an indirect wholly owned subsidiary of DENTSPLY International Inc., a Delaware corporation, herewith applies for an Extension of Patent Term under the provisions of 35 USC 156. MITS changed its name from Dentsply Anaesthetics S.a.r.l. effective January, 2001 and was the assignee of US 6,031,007 from Astra Zeneca AB recorded in the US Patent and Trademark Office September 10, 2001 at Real/Frame 012153/0068, which changed its name from Astra AB in accord with a letter to the US Patent

and Trademark Office dated July 28, 2000. Dentsply Pharmaceutical is an operating division of Dentsply International.

We include in our Application the enclosed exhibits which we believe, in addition to the remarks below, are sufficient to meet the requirements of 37 CFR 1.740(a). 37 CFR 1.740(a) requires, under the indicated subsection:

(1) A complete identification of the approved product, by appropriate chemical and generic name, physical structure or characteristics. Applicant submits as Exhibit 1 its FDA approved ORAQIX package insert which provides the required information;

(2) A complete identification of the Federal statute, including the applicable provision of law under which the regulatory review occurred. Applicant submits as Exhibit 2 the FDA's approval letter for the ORAQIX NDA 21-451 which approved the ORAQIX product under Section 505(b) of the Federal Food Drug and Cosmetic Act;

(3) An identification of the date on which the product received permission for commercial marketing or use. Applicant submits as Exhibit 3 the results of an on-line search of the FDA's Orange Book which shows the approval date of December 19, 2003 for the ORAQIX product, NDA 21-451;

(4) In the case of a drug product, an identification of each active ingredient in the product and a statement ...of when the active ingredient was approved, either alone or in combination with other active ingredients, and the provision of the law under which it was approved. Applicant submits as Exhibit 4, the ORAQIX Composition and a summary identification of when each ingredient was approved. The Exhibit was earlier submitted to the FDA as part of our NDA application.

(5) A statement that the application is being submitted within the 60 day period permitted for submission pursuant to Section 1.720(f) and an identification of the date of the last day on which the application could be submitted. Applicant submits as Exhibit 5 the required

statement, to the effect that our submittal is timely and is before the last day of permitted submission, February 17, 2004;

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue and the date of expiration. Applicant submits as Exhibit 6 a complete copy of the United States patent, which shows that the inventor is Brodin et al, the patent number is US 6,031,007, said patent issued February 29, 2000 and shall expire April 1, 2017;

(7) A copy of the patent for which the extension is being sought. As noted above, Application submits Exhibit 6 which is a complete copy, including the entire specification and claims. There are no drawings to the patent;

(8) A copy of any disclaimers, certificate of correction, receipt of maintenance fee payment or re-examination certificate issued in the patent. In response, Applicant submits as Exhibit 7 a USPTO Maintenance Fee Statement showing that the first maintenance fee was paid;

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product and a showing which lists each applicable patent claim and demonstrates the manner in which, at least one such patent claims reads on: (i) the approved product, method or using and/or method of manufacturing. Applicant submits that claims 1, 3, 4, 5, 6, 8-12 and 16 of US 6,031,007 read on the composition of the ORAQIX product. Applicant further includes Exhibit 8, a claim chart which lists the applicable claim limitations and demonstrates how each claim reads on the product by reference to the Package Insert of Exhibit 1 and Composition of Exhibit 4;

(10) Requires a statement, beginning on a new page, of the relevant dates and information pursuant to 35 USC 156(g) in order to enable the Secretary of Health and Human Services to make a determination of the applicable regulatory review period for (i) a patent claiming a human drug, including (A) the effective date of the investigational new drug (IND) application and the IND number; (B) the date on which a new drug application (NDA) was

initially submitted and the NDA number; and (C) the date on which the NDA was approved. Applicant submits as Exhibit 9 the required statement, the dates of which are extracted from Exhibit 10 described below;

(11) Requires a brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and significant dates applicable to such activities. Applicant submits as Exhibit 10 a chronology beginning with the IND 52,677, continuing as NDA 21-451 which was approved by the FDA as ORAQIX;

(12) Requires a statement beginning on a new page that in the opinion of the Applicant the patent is eligible for the extension and a statement of the length of extension claimed, including how the length of extension was determined. Applicant submits as Exhibit 11 a statement that the patent is eligible for extension and claims an extension of time of 1040 days calculated in accord with 35 USC 156.

(13) Requires a statement by the Applicant acknowledging a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of the entitlement to the extension sought.

Applicant herewith acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of the entitlement to the extension sought.

(14) Requires that the prescribed fee for receiving and acting on the Application for Extension under Section 1.20(j) of $1,120.00 be provided.

Applicant herewith approves payment of the fee and any additional required fees and requests that all fees or credits be charged to our Deposit Account 04-0780; and

(15) Requires that the name, address and telephone number of the person to whom inquiries and correspondence relating to the application for Patent Term Extension are to be directed. Applicant states that such inquires and correspondence be directed to:

James B. Bieber Esquire
DENTSPLY International Inc.
570 West College Avenue
P.O. Box 872
York, PA 17405-0872

Respectfully submitted,

James B. Bieber
Patent Attorney Reg. No. 28054

February 16, 2004

Address of signer:

DENTSPLY INTERNATIONAL INC.
570 West College Avenue
York, PA 18405-0872
(717) 849-4466

EXHIBIT 1

Local anesthetic for periodontal administration
Not for Injection

oraqix®

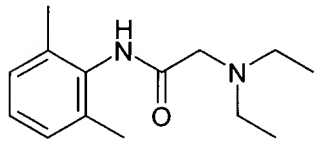
(lidocaine and prilocaine periodontal gel) 2.5%/2.5%

DESCRIPTION

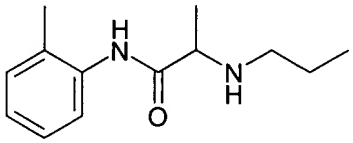
Oraqix® (lidocaine and prilocaine periodontal gel,) 2.5%/2.5% is a microemulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature, therefore both local anesthetics exist as liquid oils rather than as crystals. Oraqix® contains poloxamer excipients, which show reversible temperature-dependent gelation. Together with the lidocaine-prilocaine 1:1 mixture, the poloxamers form a low-viscosity fluid system at room temperature and an elastic gel in the periodontal pocket. Oraqix® is administered into periodontal pockets, by means of the supplied special applicator. Gelation occurs at body temperature, followed by release of the local anesthetics, lidocaine and prilocaine. The Oraqix®single-use glass cartridges deliver up to 1.7g (1.7 mL) of gel (42.5 mg of lidocaine and 42.5 mg of prilocaine). Prilocaine base and lidocaine base are both relatively hydrophilic amino-amides.

STRUCTURAL FORMULAS

Structural formulas



Lidocaine
$C_{14}H_{22}N_2O$ M.W. 234.3



Prilocaine
$C_{13}H_{20}N_2O$ M.W. 220.3

Lidocaine is chemically designated as 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide and has an octanol:water partition ratio of 43 at pH 7.4. The pKa of lidocaine is 7.86.
Prilocaine is chemically designated as N-(2-methyl-phenyl)-2-(propylamino)-propanamide and has an octanol:water partition ratio of 25 at pH 7.4. The pKa of prilocaine is 7.89.

Each gram of Oraqix® contains 25-mg lidocaine base and 25-mg prilocaine base. The gel also contains thermosetting agents (poloxamer 188 purified, poloxamer 407 purified), hydrochloric acid (pH adjustment), and purified water. The pH of Oraqix®is 7.5-8.0.

CLINICAL PHARMACOLOGY

Lidocaine and prilocaine belong to the amide class of local anesthetics. Both lidocaine and prilocaine block sodium ion channels required for the initiation and conduction of neuronal impulses, resulting in local anesthesia.

Oraqix® is applied directly into periodontal pockets to provide localized anesthesia. The onset of local anesthetic effect after application of Oraqix® occurs by 30 seconds and a longer waiting time does not enhance the anesthetic effect. Anesthetic effect, as assessed by probing of pocket depths, lasted for about 20 minutes (individual overall range 14 – 31 minutes).

PHARMACOKINETICS

Absorption: Lidocaine and prilocaine are absorbed from Oraqix®via the oral mucous membranes. After a single application of 0.9 –3.5 g Oraqix®, the mean (±SD) lidocaine and prilocaine C_{max} values were 182 (±53) and 77 (±27) ng/mL, respectively. After a total of 8 – 8.5 g Oraqix® administered as repeated applications over 3 hours, the mean (±SD) lidocaine C_{max} was 284 (±122) ng/mL, ranging between 157 and 552 ng/mL. The mean lidocaine AUC∞ was 84,000 ng·min/mL. The mean (±SD) prilocaine C_{max} was 106 (±45) ng/mL, ranging between 53 and 181 ng/mL. The mean prilocaine AUC∞ was 26,000 ng·min/mL.

The toxicities of lidocaine and prilocaine are thought to be additive. Systemic CNS toxicity may occur over a range of plasma concentrations of local anesthetics. CNS toxicity may typically be found around 5000 ng/mL of lidocaine, however a small number of patients reportedly may show signs of toxicity at approximately 1000 ng/mL. Pharmacological thresholds for prilocaine are poorly defined.

The median T_{max} of lidocaine and prilocaine was 30 minutes, ranging between 20 and 40 min., after the start of a single application of 0.9 to 3.5 g Oraqix®, and 200 minutes, ranging between 120 and 200 min., after a cumulative dose of 8.5g Oraqix® administered as repeated applications over 3 hours.

Distribution: Lidocaine and prilocaine have an intermediate degree of plasma protein binding, mainly to 1-acid glycoprotein, with a protein binding of 70% and 40%, respectively. When administered intravenously, the mean volume of distribution (for 60 kg person) at steady state for lidocaine and prilocaine were 90 L and 156 L, respectively. Oraqix®is not intended for intravenous administration. Both lidocaine and prilocaine cross the placental and blood brain barriers, presumably by passive diffusion.

Metabolism: Lidocaine and prilocaine are mainly metabolized in the liver. Prilocaine and lidocaine are not metabolized by plasma esterases.

The main metabolism of lidocaine is through N-dealkylation to monoethylglycinexylidide (MEGX) and glycinexylidide (GX), which is mainly mediated by CYP3A4. These metabolites are hydrolyzed to 2,6-xylidine, which is converted to 4-hydroxy-2,6-xylidine (mediated by CYP2A6), the major urinary metabolite in man. After a total of 8-8.5 g Oraqix® administered as repeated applications over 3 hours, the mean (±SD) 2,6-xylidine C_{max} was 18 (±8.4) ng/mL ranging between 8 and 32 ng/mL. The mean 2,6-xylidine AUC∞ was 9800 ng.min/mL (±6370), ranging between 3480-24,580 ng/min/mL). MEGX has an antiarrhythmic and convulsant activity similar to that of lidocaine and a somewhat longer half-life. GX has a weak antiarrhythmic effect but lacks convulsant activity and has a half-life of about 10 h.

Prilocaine is split at the amide linkage to o-toluidine, which is converted further to 4- and 6- hydroxytoluidine. The prilocaine metabolite o-toluidine and the hydroxylated metabolites of o-toluidine are excreted mainly in the urine. o-Toluidine has been shown to be carcinogenic in several animal models. After a total of 8 – 8.5 g Oraqix® was administered as repeated applications over 3 hours, the mean (±SD) o-toluidine C_{max} was 25 (±11) ng/mL ranging between 13 and 44 ng/mL. The mean o-toluidine AUC^{∞} was 9200 ng·min/mL. The median T_{max} was 220 minutes, ranging between 90 and 240 min. In addition, o-Toluidine can cause the formation of methemoglobin (metHb) following treatment with prilocaine. Individual maximum blood concentrations of metHb increased from 0 - 1.1% up to 0.8 – 1.7% following administration of the maximum recommended dose of 8.5 g Oraqix® administrated as repeated applications over 3 hours. The Tmax of metHb ranged from 1 to 4 hours. Normally, <1 % of the total hemoglobin is in the form of metHb.(see OVERDOSAGE). Patients with glucose-6-phosphate dehydrogenase deficiencies, and patients taking oxidizing drugs such as antimalarials and sulfonamides are more susceptible to drug-induced methemoglobinemia. (See WARNINGS)

Elimination: Lidocaine and prilocaine have systemic clearances of 0.95 and 2.37 L/min, respectively, after intravenous administration as single agents. The terminal half-life of both drugs after intravenous administration as single agents is 1.6 h. Oraqix® is not intended for intravenous administration.

However, after application of Oraqix® to the periodontal pockets the mean (±SD) terminal lidocaine half-life was 3.6 (±1.3) hours, ranging between 2.2 and 6.5 h. The mean (±SD) terminal prilocaine half-life was 2.8 (±1.0) hours, ranging between 2.0 to 5.7 h. For the metabolite o-toluidine the mean terminal half-life was 4.0 (±1.1) hours, ranging between 2.0 and 5.7 hours. For the metabolite 2,6-xylidine the mean terminal half-life was 8.0 (±4.0) hours, ranging between 3.7 and 18.3 hours.

Linearity: The increase in C_{max} of both lidocaine and prilocaine is proportional (or less than proportional) to the dose after single application of Oraqix®. The C_{max} after a cumulative dose of 8.5 g Oraqix® administered as repeated applications over 3 hours, (i.e. the highest recommended dose, corresponding to 212.5 mg each of lidocaine and prilocaine base), is lower than that extrapolated from the proportional increase in plasma concentrations at lower doses.

Pediatrics: The pharmacokinetics of lidocaine and prilocaine after Oraqix® administration have not been studied in pediatric patients.

Geriatrics : The pharmacokinetics of lidocaine and prilocaine after Oraqix® administration have not been studied in geriatric patients.

However, intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). No studies on the intravenous pharmacokinetics of prilocaine in elderly patients have been performed.

Special populations: No pharmacokinetic studies were conducted to specifically address special populations. Renal Impairment: Lidocaine and prilocaine and their metabolites are known to be excreted by the kidney, and the metabolites may accumulate in patients with impaired renal function. Hepatic Impairment: The half-life of lidocaine may be prolonged two-fold or more in patients with liver dysfunction. Liver dysfunction may also alter prilocaine pharmacokinetics. Because of their inability to metabolize local anesthetics normally, patients with severe hepatic disease, are at a greater risk of developing toxic plasma concentrations of lidocaine and prilocaine.

CLINICAL STUDIES

A total of 337 patients (146 men and 191 women; 169 Oraqix® and 168 placebo) were studied in three randomized, double-blind, placebo-controlled trials. Subjects received a median dose of approximately 1 cartridge (1.7g gel), ranging from ¼ - 2½ cartridges per quadrant treated. The primary objective of these clinical studies was to estimate the analgesic effect of Oraqix® by asking subjects to rate their pain on a continuous visual analog scale (VAS) from 0 (no pain) to 100 mm (worst pain imaginable). Patients were asked to report overall procedural pain 5 minutes following manual scaling and/or root planing (SRP) in a single quadrant that had been pre-treated with Oraqix® or placebo (vehicle only, without lidocaine or prilocaine). In all three studies, subjects who were given Oraqix® reported less pain during the procedure than those given placebo. Study B3 recruited patients with a known sensitivity to mechanical probing of dental pockets, whereas in studies B1 and B2, this was not a requirement. Results of B1, B2 and B3 are summarized below.

Visual Analog Pain Scale (100 mm scale)

Visual Analog Pain Scale

Study (no of patients)	Oraqix® Median VAS	Placebo Median VAS
B1 (n=122)*	7	17
B2 (n=130)*	5	13
B3 (n=85)*	11	27

*$p<0.05$

A secondary objective was to compare individual patient estimates of pain on a 5-step categorical Verbal Rating Scale (VRS) which included the following categories: no pain, mild pain, moderate pain, severe pain, and very severe pain. The results of those who reported no pain or mild pain are shown in the next table.

Verbal Rating Scale

Number of Patients Reporting "no pain" or "mild pain" during SRP

Study (no of patients)	Oraqix®	Placebo
B1 (n=122)*	57 (90%)	38 (64%)
B2 (n=130)	49 (78%)	51 (76%)
B3 (n=85)*	30 (70%)	20 (48%)

* $p<0.05$ in the statistical test of the full five categorical scale

INDICATIONS AND USAGE

Oraqix® is indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing.

CONTRAINDICATIONS

Oraqix® is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to any other component of the product.

WARNINGS

Prilocaine can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents. Methemoglobinemia has also been reported in a few cases in association with lidocaine treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Oraqix® should not be used in those patients with congenital or idiopathic methemoglobinemia and in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents. Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia are characterized by a slate grey cyanosis seen in , e.g., buccal mucous membranes, lips and nail beds. In severe cases symptoms may include central cyanosis, headache, lethargy, dizziness, fatigue, syncope, dyspnea, CNS depression, seizures, dysrhythmia and shock. Methemoglobinemia should be considered if central cyanosis unresponsive to oxygen therapy occurs, especially if metHb-inducing agents have been used. Calculated oxygen saturation and pulse oximetry are inaccurate in the setting of methemoglobinemia. The diagnosis can be confirmed by an elevated methemoglobin level measured with co-oximetry. Normally, metHb levels are <1%, and cyanosis may not be evident until a level of at least 10% is present. The development of methemoglobinemia is generally dose related. The individual maximum level of metHb in blood ranged from 0.8% to 1.7% following administration of the maximum dose of 8.5 g Oraqix®.

Management of Methemoglobinemia: Clinically significant symptoms of methemoglobinemia should be treated with a standard clinical regimen such as a slow intravenous injection of methylene blue at a dosage of 1-2 mg/kg given over a five minute period.

Patients taking drugs associated with drug-induced methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine are also at greater risk for developing methemoglobinemia.
Treatment with Oraqix® should be avoided in patients with any of the above conditions or with a previous history of problems in connection with prilocaine treatment.

PRECAUTIONS

General:

DO NOT INJECT

Oraqix® should not be used with standard dental syringes. Only use this product with the Oraqix® Dispenser, which is available from DENTSPLY Pharmaceutical.

Allergic and anaphylactic reactions associated with lidocaine or prilocaine can occur. These reactions may be characterized by urticaria, angioedema, bronchospasm, and shock. If these reactions occur they should be managed by conventional means.

Oraqix® coming in contact with the eye should be avoided because animal studies have demonstrated severe eye irritation. A loss of protective reflexes may allow corneal irritation and potential abrasion. If eye contact occurs, immediately rinse the eye with water or saline and protect it until normal sensation returns. In addition, the patient should be evaluated by an ophthalmologist, as indicated.

Patients allergic to paraminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine and/or prilocaine. However, Oraqix® should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine and prilocaine.

Information for Patients: Patients should be cautioned to avoid injury to the treated area, or exposure to extreme hot or cold temperatures, until complete sensation has returned.

Drug Interactions: Oraqix® should be used with caution in combination with dental injection anesthesia, other local anesthetics, or agents structurally related to local anesthetics, e.g., Class 1 antiarrhythmics such as tocainide and mexiletine, as the toxic effects of these drugs are likely to be additive and potentially synergistic. Patients taking drugs associated with drug-induced methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine are also at greater risk for developing methemoglobinemia. (see OVERDOSAGE).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

Carcinogenesis - Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or prilocaine. Chronic oral toxicity studies of o-toluidine, a metabolite of prilocaine, have shown that this compound is a carcinogen in both mice and rats. The tumors associated with o-toluidine included hepatocarcinomas/adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/ adenomas in female rats. These findings were observed at the

lowest tested dose of 150 mg/kg/day or greater over two years (estimated daily exposures in mice and rats were approximately 6 and 12 times, respectively, the estimated exposure to o-toluidine at the maximum recommended human dose of 8.5g of Oraqix® gel on a mg/m^2 basis). Thus, the no effect dose is less than 6 to 12 times the estimated exposure to o-toluidine at the maximum recommended human dose, assuming 100% bioavailialbility of prilocaine from the Oraqix® gel Complete conversion of prilocaine to its metabolite o-toluidine on a molar basis is assumed. This gives a conversion on a weight basis of about 50% for prilocaine base (dependent on the molecular weights, i.e. 220 for prilocaine base and 107 for o-toluidine).

Mutagenesis - The mutagenic potentials of lidocaine and prilocaine have been tested in the Ames Salmonella reverse mutation assay, an in vitro chromosome aberrations assay in human lymphocytes and in an in vivo mouse micronucleus assay. There was no indication of any mutagenic effects for either compound in these studies.

o-Toluidine, a metabolite of prilocaine, was positive in Escherichia coli DNA repair and phage-induction assays. Urine concentrates from rats treated orally with 300 mg/kg o-toluidine were mutagenic to Salmonella typhimurium in the presence of metabolic activation. Several other tests on o-toluidine, including reverse mutations in five different Salmonella typhimurium strains with or without metabolic activation, and single strand breaks in DNA of V79 Chinese hamster cells, were negative.

IMPAIRMENT OF FERTILITY: The effect of lidocaine on fertility was examined in the rat model. Administration of 30 mg/kg, s.c. (180 mg/m^2 or 1.4 fold the maximum recommended human oral dose for one treatment session assuming 100% bioavailability of lidocaine) to the mating pair did not produce alterations in fertility or general reproductive performance of rats. There are no studies that examine the effect of lidocaine or prilocaine on sperm parameters. The effects of prilocaine on fertility was examined in rats treated for 8 months with 10 or 30 mg/kg, s.c. lidocaine or prilocaine (60 mg/m^2 and 180 mg/m^2 on a body surface area basis, respectively up to 1.4-fold the maximum recommended exposure for a single procedure assuming 100% bioavailability of lidocaine and prilocaine). This time period encompassed 3 mating periods. There was no evidence of altered fertility.

USE IN PREGNANCY:

Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in rats with lidocaine, prilocaine and a 1:1 (weight:weight) mixture of the two compounds. There was no evidence of harm to the fetus at subcutaneous doses of up to 30 mg/kg lidocaine (estimated exposure was approximately equivalent to the expected lidocaine exposure at the maximum recommended human dose of Oraqix® gel on a mg/m^2 basis). Following intramuscular prilocaine doses of up to 300 mg/kg (estimated exposure was approximately 11 times the expected prilocaine exposure at the maximum recommended human dose of Oraqix® gel on a mg/m^2 basis), there was no evidence of impaired fertility or harm to the fetus. Similarly, subcutaneous administration of a lidocaine and prilocaine mixture of 40 mg/kg of each compound (estimated exposures were approximately 1.5 times the expected

lidocaine and prilocaine exposures at the maximum recommended human dose of Oraqix® gel on a mg/m^2 basis) produced no teratogenic, embryotoxic, or fetotoxic effects. Reproductive toxicology studies of lidocaine were also conducted in rabbits. There was no evidence of harm to the fetus at a dose of 5 mg/kg, s.c. (60 mg/m^2). Treatment of rabbits with 15 mg/kg (180 mg/m^2) produced evidence of maternal toxicity and evidence of delayed fetal development, including a non-significant decrease in fetal weight (7%) and an increase in minor skeletal anomalies (skull and sternebral defects, reduced ossification of the phalanges). The effects of lidocaine and prilocaine on post-natal development was examined in rats treated for 8 months with 10 or 30 mg/kg, s.c. lidocaine or prilocaine (60 mg/m^2 and 180 mg/m^2 on a body surface area basis, respectively up to 1.4-fold the maximum recommended exposure for a single procedure). This time period encompassed 3 mating periods. There was no evidence of altered post-natal development in any offspring, however, both doses of either drug significantly reduced the average number of pups per litter surviving until weaning of offspring from the first 2 mating periods. All the above calculations of exposure are assuming 100% bioavailability of lidocaine and prilocaine after Oraqix® administration. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Oraqix® should be used during pregnancy only if the benefits outweigh the risks.

Reproduction studies on the Oraqix® drug product, including the inactive ingredients, have not been conducted.

Nursing Mothers: Lidocaine and, possibly, prilocaine are excreted in breast milk. Caution should be exercised when Oraqix® is administered to nursing women.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Very young children are more susceptible to methemoglobinemia. There have been reports of clinically significant methemoglobinemia in infants and children following excessive applications of lidocaine 2.5% and prilocaine 2.5% topical cream (See WARNINGS).

Geriatric Use: Of the total number of subjects in clinical studies of Oraqix®, 7% were aged 65 and over, while 1% were aged 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Although no major differences in adverse events between Oraqix® and placebo treated subjects were observed, all patients in the placebo controlled studies received either Oraqix® or a placebo gel (consisting of the vehicle in Oraqix® without lidocaine or prilocaine). Therefore, it is not possible to determine if adverse events in each treatment group were attributable to the inactive ingredients comprising the Oraqix® vehicle or if

adverse event rates were higher than expected background rates. Therefore, a causal relationship between the reported adverse reactions and Oraqix® could neither be established nor ruled out.

Following SRP treatment with Oraqix® in 391 patients, the most frequent adverse events were local reactions in the oral cavity (see following table). These events, which occurred in approximately 15% of patients, included pain, soreness, irritation, numbness, vesicles, ulcerations, edema and/or redness in the treated area. Of the 391 patients treated with Oraqix®, five developed ulcerative lesions and two developed vesicles of mild to moderate severity near the site of SRP. In addition, ulcerative lesions in or near the treated area were also reported for three out of 168 patients who received placebo. Other symptoms reported in more than one patient were headache, taste perversion, nausea, fatigue, flu, respiratory infection, musculoskeletal pain and accident/injury.

Table 1. Number (percent) of patients with adverse events occurring in more than one patient in any of the treatment groups.

Each patient is counted only once per adverse event. The occurrence in a single patient is included in this table if the same symptom has been seen in at least one patient in another group.

System Organ Class *Preferred Term*	Oraqix® gel* N=391 n (%)	Placebo (vehicle only) gel N=168 n (%)	Lidocaine injection* N=170 n (%)
MUSCULO-SKELETAL SYSTEM DISORDERS			
Myalgia	1 (0)	2 (1)	
Arthralgia and/or Arthropathy	1 (0)	1 (1)	
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS			
Headache	8 (2)	3 (2)	5 (3)
Dizziness	1 (0)	1 (1)	1 (1)
SPECIAL SENSES OTHER, DISORDERS			
Taste Perversion[1]	8 (2)	1 (1)	
GASTRO-INTESTINAL SYSTEM DISORDERS			
Nausea	3 (1)		1 (1)
RESPIRATORY SYSTEM DISORDERS			
Respiratory Infection	2 (1)		1 (1)
Rhinitis		2 (1)	
BODY AS A WHOLE – GENERAL DISORDERS			

Accident and/or Injury	2 (1)	2 (1)	
Fatigue	3 (1)		2 (1)
Flu-Like Disorder	2 (1)		
Pain (remote from application site)	1 (0)	1 (1)	1 (1)
APPLICATION SITE DISORDERS**			
Anesthesia local	2 (1)		
Application Site Reaction***	53 (14)	20 (12)	

[1]includes complaints of bad or bitter taste lasting for up to 4 hours after administration of Oraqix®

* in a cross-over study, 170 subjects received either Oraqix® or lidocaine injection 2% in each test period

** i.e.,symptoms in the oral cavity

*** includes pain, soreness, irritation, numbness, ulcerations, vesicles, edema, abscess and/or redness in the treated area

Allergic Reactions: Allergic and anaphylactic reactions associated with lidocaine or prilocaine can occur. They may be characterized by urticaria, angioedema, bronchospasm, and shock. If they occur, they should be managed by conventional means.

OVERDOSAGE

Local anesthetic toxicity emergency: Oraqix® used at the recommended doses is not likely to cause toxic plasma levels of lidocaine or prilocaine. However, if other local anesthetics are administered at the same time, e.g. topically or by injection, the toxic effects are thought to be additive and could result in an overdose with systemic toxic reactions. There is generally an increase in severity of symptoms with increasing plasma concentrations of lidocaine and/or prilocaine. Systemic CNS toxicity may occur over a range of plasma concentrations of local anesthethics. CNS toxicity may typically be found around 5000 ng/mL of lidocaine, however a small number of patients reportedly may show signs of toxicity at approximately 1000 ng/mL. Pharmacological thresholds for prilocaine are poorly defined. Central nervous system (CNS) symptoms usually precede cardiovascular manifestations. The plasma level of lidocaine observed after the maximum recommended dose (5 cartridges) of Oraqix® in 11 patients exposed over 3 hours ranged from 157-552 ng/mL with a mean of 284 ng/mL ± 122 SD. The corresponding figure for prilocaine was 53-181 ng/mL with a mean of 106 ± 45 SD. (see CLINICAL PHARMACOLOGY, Absorption).

Systemic adverse effects of lidocaine and/or prilocaine are manifested by central nervous system and/or cardiovascular symptoms.

Clinical symptoms of systemic toxicity include CNS excitation and/or depression (light-headedness, hyperacusis, visual disturbances, muscular tremors, and general convulsions). Lidocaine and/or prilocaine may cause decreases in cardiac output, total

peripheral resistance and mean arterial pressure. These changes may be attributable to direct depressant effects of these local anesthetic agents on the cardiovascular system. Cardiovascular manifestations may include hypotension, bradycardia, arrhythmia, and cardiovascular collapse.

Management of Local Anesthetic Emergencies: Should severe CNS or cardiovascular symptoms occur, these may be treated symptomatically by, for example, the administration of anticonvulsive drugs, respiratory support and/or cardiovascular resuscitation as necessary.

Methemoglobinemia: Prilocaine can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents. Methemoglobinemia has also been reported in a few cases in association with lidocaine treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Very young patients, patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Signs and symptoms of methemoglobinemia may be delayed some hours after exposure Initial signs and symptoms of methemoglobinemia are characterized by a slate grey cyanosis seen in , e.g., buccal mucous membranes, lips and nail beds. In severe cases symptoms may include central cyanosis, headache, lethargy, dizziness, fatigue, syncope, dyspnea, CNS depression, seizures, dysrhythmia and shock. Methemoglobinemia should be considered if central cyanosis unresponsive to oxygen therapy occurs, especially if metHb-inducing agents have been used. Calculated oxygen saturation and pulse oximetry are inaccurate in the setting of methemoglobinemia. The diagnosis can be confirmed by an elevated methemoglobin level measured with co-oximetry. Normally, metHb levels are <1%, and cyanosis may not be evident until a level of at least 10% is present. The development of methemoglobinemia is generally dose related. The individual maximum level of metHb in blood ranged from 0.8% to 1.7% following administration of the maximum dose of 8.5 g Oraqix® .

Management of Methemoglobinemia: Clinically significant symptoms of methemoglobinemia should be treated with a standard clinical regimen such as a slow intravenous injection of methylene blue at a dosage of 1-2 mg/kg given over a five minute period.

DOSAGE AND ADMINISTRATION

Apply Oraqix® on the gingival margin around the selected teeth using the blunt-tipped applicator included in the package. Wait 30 seconds, then fill the periodontal pockets with Oraqix® using the blunt-tipped applicator until the gel becomes visible at the gingival margin. Wait another 30 seconds before starting treatment. A longer waiting time does not enhance the anesthesia. Anesthetic effect, as assessed by probing of pocket depths, has a duration of approximately 20 minutes (individual overall range 14 – 31 minutes). If the anesthesia starts to wear off, Oraqix® may be re-applied if needed. The maximum recommended dose of Oraqix® at one treatment session is 5 cartridges, i.e., 8.5g gel. Application of Oraqix® into periodontal pockets without prior application to the gingival margin was tested in one open-label study. This method of application appears to be safe; however, its efficacy has not been tested.

Typically, 1 cartridge (1.7g) or less of Oraqix® will be sufficient for one quadrant of the dentition.

When administered, Oraqix® should be a liquid. If it has formed a gel, it should be placed in a refrigerator (do not freeze) until it becomes a liquid again. When in the liquid state, the air bubble visible in the cartridge will move if the cartridge is tilted.

DO NOT INJECT
Oraqix® should not be used with standard dental anesthetic syringes. Only use this product with the Oraqix® Dispenser, which is available from DENTSPLY Pharmaceutical.

HOW SUPPLIED
Oraqix® (lidocaine and prilocaine periodontal gel), 2.5%/2.5%, is supplied in dental cartridges that provide 1.7g gel. Individually blister-packaged cartridges of Oraqix® are distributed in a carton of 20 (NDC 66312-110-20). Each individual blister package also contains a sterile blunt-tipped applicator. Each blunt-tipped applicator is for single use only.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature.]

At temperatures below +5°C Oraqix® may become opaque. This opacity will disappear when the cartridge is warmed to room temperature.

DO NOT FREEZE. Some components of Oraqix® may precipitate if cartridges are frozen. Cartridges should not be used if they contain a precipitate.
Do not use dental cartridge warmers with Oraqix®. The heat will cause the product to gel.

Rx only

Manufactured for:
DENTSPLY Pharmaceutical
3427 Concord Road
York, PA 17402
By:
AstraZeneca AB
Karlskoga
Sweden

EXHIBIT 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-451

Dentsply Pharmaceutical
3427 Concord Road
York, PA 17402

Attention: Karenlee Modric,
Director, Regulatory Affairs and Quality Assurance

Dear Ms. Modric:

Please refer to your new drug application (NDA) dated January 22, 2002, received January 22, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oraqix (Lidocaine and prilocaine periodontal gel) 2.5%/2.5%.

We acknowledge receipt of your submissions dated February 1, March 8, and 14, April 1, May 17, June 24 and 27, July 17, August 16, and 26, September 20, October 15, November 11, 13, 18 and 21, and December 20, 2002, February 12, March 28 and 31, April 14, 15 and 30, May 2, June 19, July 24, September 17, November 21, and December 11, 12, and 18, 2003.

The June 19, 2003, submission constituted a complete response to our November 20, 2002, action letter.

This new drug application provides for the use of Oraqix (Lidocaine and prilocaine periodontal gel) 2.5%/2.5% for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the attached labeling (package insert) and labeling submitted December 12, 2003 (immediate container and carton labels) with the minor revisions noted below.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert), and the labeling submitted December 12, 2003 (immediate container and carton labels) with the following minor revisions.

1. On the Immediate Carton (foil blister) labels:

   Switch the location of the phrase "Rx Only" with the phrase "1.7 g" ("1.7 g" currently appears on the line with the word "Use" and it appears that this might be an instruction

to "use 1.7 g"). Also, add the word "gel" after the phrase "1.7 g" (e.g., to read "1.7 g gel").

2. On the Immediate Container (Cartridge) label:

   Right adjust the phrase "1.7 g" and add the word "gel" following it so it is clear that the 1.7 g refers to the amount of gel in the cartridge and it is separated from the word "Use" as much as possible.

3. In the Package Insert:

   a. Convert the "max" portion of the phrases "Cmax" and "Tmax" to subscripts.

   b. Ensure that all references to the brand name Oraqix are followed by the appropriate symbology (e.g.,®) consistently throughout the labeling.

   c. Update the duration of action of the anesthetic effect range from the current 25-75% quartile to the 10-90% range.

4. In all Oraqix labeling:

   a. Ensure that the newly agreed upon established name ["Oraqix (lidocaine and prilocaine periodontal gel) 2.5%/2.5%"] is consistently used throughout the labeling.

   b. Adjust the fonts or other appropriate features accordingly (not simply the point size of the typeface, since different fonts have different prominences, etc.) so that the established name *appears* at half the prominence of the brand name. We note that in the current versions, different fonts are utilized so that even though the point sizes listed appear to be in the appropriate ratio, the sizes of the letters do not allow for the appropriate prominence of the established name.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically, according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-451." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated December 19, 2003. This commitment is listed below.

Complete a Segment III Reproductive Toxicology study on prilocaine in a single species as described in the ICH-S5A Guidance to Industry. The adverse effects to be assessed will include measurements of altered growth and development and functional deficits in the offspring,

including behavior, maturation (puberty) and reproduction (F1). Sensory functions, reflexes and behavioral responses will be assessed in the F1 generation.

Protocol Submission:	by May 2004
Study Start:	by July 2004
Final Report Submission:	by July 2005

We also remind you of your agreements to the following:

1. Provide, on at least an annual basis, all reports of product misuse, product defects (e.g. defective collars), device failures, or other events that may relate to the potential for accidental injection of Oraqix. Submit such information even if no adverse occurrences are observed.

2. Provide a plan for education of practitioners during the rollout of Oraqix. This educational program should include instruction on the proper use of Oraqix, particularly with respect to the need to avoid injection of Oraqix.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0-5 years and deferring pediatric studies for ages 6-17 years for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Ron Zentz
02/11/2004 12:18 AM

To: Jim Bieber/Dentsply@Dentsply
cc:
Subject: Oraqix

Jim,

Here is a copy of the approval letter from FDA. In the first paragraph it identifies the section of the Code under which the NDA was file and approved (section 505(b)). I reviewed the list again on page 2700-19 of the info you sent to me. I think this is the only thing that was missing that I can provide. The other components are in the package insert and chronologies already sent to you. The other things relate directly to patent and claims.

Let me know if you see anything else that I can provide. Thanks again for your help Jim.

Ron

NDA 21-451 Approval ltr only 12-19-0:

Ronald R. Zentz, RPh, DDS
Director of Clinical Affairs
DENTSPLY Pharmaceutical
3427 Concord Rd
York, PA 17402

PH 717 757-0206
Mobile 717 887-1456
FX 717 757-5572
rzentz@dentsply.com

EXHIBIT 3

Search results from the "Rx" table for query on "021451."

Active Ingredient:	LIDOCAINE; PRILOCAINE
Dosage Form;Route:	Gel; Periodontal
Proprietary Name	ORAQIX
Applicant:	DENTSPLY PHARM
Strength:	2.5%;2.5%
Application Number:	021451
Product Number:	001
Approval Date:	DEC 19, 2003
Reference Listed Drug:	Yes
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: Click Here

Thank you for searching the **Electronic Orange Book**

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Proprietary Name Search Results from "Rx" table for query on "oraqix."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Ap
021451		Yes	LIDOCAINE; PRILOCAINE	Gel; Periodontal	2.5%;2.5%	ORAQIX	DE PH

Thank you for searching the Electronic Orange Book

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Patent and Exclusivity Search Results from query on 021451 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021451	001	NDF	DEC 19,2006

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

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EXHIBIT 4

COMPOSITION

Ingredient	Quantity	Function	Standard
Lidocaine	25 mg	Active ingredient; local anesthetic compound	Reference to NDA 19-941 for EMLA
Prilocaine	25 mg	Active ingredient; local anesthetic compound	Reference to NDA 19-941 for EMLA
Poloxamer 188 Purified	55 mg	Surfactant and viscosity controlling agent	AstraZeneca, P104137-1.0
Poloxamer 407 Purified	155 mg	Surfactant and viscosity controlling agent	AstraZeneca, P104138-1.0
Hydrochloric acid	q.s.	pH adjusting agent	Ph Eur, NF
Water Purified	to 1000 mg	Solvent	Ph Eur, USP

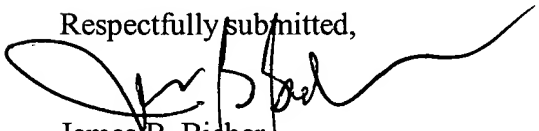
Note: None of the product components are of animal origin.

Exhibit 5

Statement That Patent Term Extension Application for US 6,031,007 is Timely Filed

Applicant, MITS and DENTSPLY International Inc. state that the approval of its NDA for ORAQIX product described and claimed in US 6,031,007 was on December 19, 2003. Applicant states that this Application for Patent Term Extension is submitted within a 60 day period permitted for submission pursuant to Section 1.720(f) the last day of said period being February 17, 2004.

Respectfully submitted,



James B. Bieber
Patent Attorney Reg. No. 28054

February 13, 2004

Address of signer:

DENTSPLY INTERNATIONAL INC.
570 West College Avenue
York, PA 18405-0872
(717) 849-4514

EXHIBIT 6

US006031007A

United States Patent [19]

Brodin et al.

[11] Patent Number: 6,031,007

[45] Date of Patent: Feb. 29, 2000

[54] **PHARMACEUTICAL COMPOSITION WITH ANAESTHETIC EFFECT**

[75] Inventors: **Arne Brodin**, Södertälje, Sweden; **Raymond Fynes**, Mississauga, Canada; **Lars Heijl**, Lerum, Sweden; **Adela Nyqvist-Mayer**, Tullinge, Sweden; **Marie Scherlund**, Bromma, Sweden

[73] Assignee: **Astra AB**, Sweden

[21] Appl. No.: **08/875,888**

[22] PCT Filed: **Apr. 1, 1997**

[86] PCT No.: **PCT/SE97/00566**

§ 371 Date: **Aug. 6, 1997**

§ 102(e) Date: **Aug. 6, 1997**

[87] PCT Pub. No.: **WO97/38675**

PCT Pub. Date: **Oct. 23, 1997**

[30] **Foreign Application Priority Data**

Apr. 12, 1996 [SE] Sweden 9601421

[51] **Int. Cl.**[7] **A61K 9/06**

[52] **U.S. Cl.** **514/716**; 514/626; 514/772; 514/817; 514/818; 514/900

[58] **Field of Search** 514/626, 716, 514/772, 817, 818, 900

[56] **References Cited**

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Nyqvist–Mayer et al, J Pharmaceutical Sciences, 75(4) pp. 365–373, Apr. 1986.

Primary Examiner—Rebecca Cook

Attorney, Agent, or Firm—Michael A. Sanzo; Vinson & Elkins L.L.P.

[57] **ABSTRACT**

The invention is directed to a novel pharmaceutical composition comprising one or more local anaesthetics in oil form, one or more surfactants, water and optionally a taste masking agent. The novel composition is advantageously used as a local anaesthetic for pain relief within the oral cavity.

17 Claims, No Drawings

PHARMACEUTICAL COMPOSITION WITH ANAESTHETIC EFFECT

This is a 371 of PCT/SE97/00566 filed Apr. 1, 1997.

THE FIELD OF THE INVENTION

The present invention is directed to a new pharmaceutical composition and its use in therapy, particularly as an anaesthetic for use on mucous membranes and particularly within the oral cavity.

BACKGROUND AND PRIOR ART

It is estimated that approximately 10–13% of the population suffers from periodontal diseases with pathological periodontal pockets. In order to eliminate or control the disease and arrest further periodontal tissue destruction, periodontal pockets need repeated subgingival mechanical debridement/cleansing. The number of periodontal pockets in a patient may vary as can the pocket depth measurement. Approximately 40% of all periodontal scaling procedures performed involve some kind of anaesthesia.

Accumulation of bacterial plaque on teeth and in the gingival sulcus elicits an inflammatory response in the marginal gingiva which may spread in an apical direction and result in loss of tooth support with the formation of periodontal pockets. The object of mechanical debridement of periodontal pockets is to control and arrest further destruction of tooth support by removal of plaque and calculus from within the pockets.

The majority of the scaling procedures are performed by hygienists. The main use of anaesthesia techniques used in conjunction with periodontal scaling is either a nerve block or infiltration. Infiltration anaesthesia is either carried out alone or in combination with topical anaesthesia, mainly jelly, ointment or spray. However, the problem with existing topical products are lack of efficacy due to inadequate depth of penetration, too short duration and difficulties in administration due to spread, taste etc. EP 244 118 discloses a controlled release drug delivery system for placement in the periodontal pocket, having a plurality of discrete microparticles consisting of a rate-controlling polymer matrix having a drug dispersed therein, said microparticles being in the range of 10–500 μm. EP 241 178 also discloses a controlled release drug delivery system for placement in the periodontal pocket, which composition comprises solid particles having an average size of 1–500 μm. However, the drug delivery systems disclosed in both these prior art patents are deviced for administration of a medicament for a longer period of time. Thus the drug delivery systems of EP 244 118 and EP 241 178 are not suitable for use in pain management in conjunction with minor surgical procedures, where a fast onset of action and relatively short duration is required.

Thus, the problem underlying the present invention is to provide a pharmaceutical composition which would provide effective pain relief in conjunction with periodontal scaling and root planing following local administration. In other words, the object of the invention is to provide a local anaesthetic that can be applied in a facile manner in the oral cavity, and more precisely within periodontal pockets. A further object of the invention is to provide a pharmaceutical composition having a short onset time and an adequate duration for the intended procedure, with no inconvenient anaesthesia.

OUTLINE OF THE INVENTION

The problem identified above has now been solved by providing a new pharmaceutical composition which preferably is in form of an emulsion, more preferably in form of a microemulsion, comprising the following ingredients:

(i) One or more local anaesthetics in oil form in the final composition;

(ii) one or more surfactants, together present in an amount effective to produce a homogenous formulation; and

(iii) water up to 100% by weight, based on the total weight of the composition.

The local anaesthetic in the final composition is one or more local anaesthetics in oil form as such, or a eutectic mixture formed by two or more local anaesthetics. The amount of the local anaesthetic in the oil phase depends on the pH-value of the formulation.

In a particularly preferred embodiment of the invention the local anaesthetic is a eutectic mixture of lidocaine base and prilocaine base.

In a further embodiment of the invention a eutectic mixture may also be formed by two or more substances, where at least one of these substances is a local anaesthetic.

The amount of the local anaesthetic or mixture of local anaesthetics is preferably in the range 0.5–20% by weight, more preferably in the range 2–7% by weight, based on the total weight of the composition.

The local anaesthetic(s) in the final composition are present in a non-solid form.

By the wording "surfactant" we mean any agent that acts as a solubilizer and/or as an emulsifier and/or as a thickening agent with thermoreversible gelling properties. The wording surfactant is also intended to include thickening agents without thermoreversible properties. If only one surfactant is used in the composition, it must be selected with care and in suitable amounts so that it acts both as a solubilizer and/or as an emulsifier, as well as a thickening agent with thermoreversible gelling properties. If more than one surfactant is present in the composition, at least one of the surfactants should have thermoreversible gelling properties. The total amount of the surfactant(s) should be present in an amount effective to produce a homogenous formulation.

The surfactants are preferably selected from non-ionic surfactants, more preferably from any non-ionic poloxamer known in the art.

Poloxamers are synthetic block copolymers of hydrophilic ethylene oxide chains and hydrophobic propylene oxide chains, having the general formula $HO—[C_2H_4O]_a—[C_3H_6O]_b—[C_2H_4O]_a—H$, a and b representing the number of the hydrophilic and hydrophobic chains respectively.

By choosing the surfactant(s) having hydrophobic and hydrophilic domains in appropriate amounts, in combination with an appropriate amount of the local anaesthetic or mixture of local anaesthetics, it is possible to achieve a composition having suitable thermoreversible gelling properties, i.e. the system remains less viscous at room temperature, and upon application into a periodontal pocket the viscosity of the composition is increased. In other words, the pharmaceutical composition according to the present invention is less viscous at room temperature. Above this temperature the composition is more viscous, providing the advantage of remaining in the periodontal pockets for the time necessary to induce local anaesthesia. The change in viscosity is reversible with temperature.

In a particularly preferred embodiment of the invention the surfactant is one or more of Lutrol F68®, which also has the name poloxamer 188 and wherein a=80 and b=27, and Lutrol F127®, which also has the name poloxamer 407 and wherein a=101 and b=56, the definitions being in accordance with USP (1995) NF18, p. 2279. Lutrol F68® and Lutrol F127® are commercially available from BASF.

In a further preferred embodiment of the invention the surfactant Arlatone 289® is used, which also has the name polyoxyethylene hydrogenated castor oil, as well as Adinol CT95® which is sodium N-methyl N-cocoyl taurate.

The total amount of surfactant(s) is preferably present in an amount of up to 50% by weight, based on the total weight of the composition.

The pH-value of the pharmaceutical composition is adjusted with suitable acid or base in such a way that the final pH-value for the composition is:

(A) pH≧[pK_a (local anaesthetic)—1.0] if the composition comprises one local anaesthetic; or

(B) pH ≧[pK_a (local anaesthetic with the lowest pK_a value)—1.0] if the composition comprises two or more local anaesthetics.

Preferably the pH is over 7.5.

Since local anaesthetics by nature have an unpleasant bitter taste, one or more taste masking agents may optionally be added to the pharmaceutical composition. The choice of taste masking agents will be appreciated by a person skilled in the art, but as an example any fruit flavours may be mentioned.

By topical application within the periodontal pocket, local anaesthesia is achieved in a very localised area, without causing the often extensive soft tissues such as the tongue, cheek and lips, to get anaesthetized which is often the case with infiltration anaesthesia. Preferably the composition is applied into a periodontal pocket by means of a blunt needle, thereby facilitating the administration of the anaesthetic and giving an increased patient comfort.

The pharmaceutical composition of the present invention has a fast onset of action being from seconds and up to approximately 5–15 minutes. The onset time is most preferably from seconds and up to approximately 5 minutes.

For the definition of emulsions, we refer to *Pharmaceutics, The Science of Dosage Form Design*, 1988, p. 109–110, by ME Aulton.

The pharmaceutical composition according to the present invention is preferably a microemulsion. By microemulsion we mean a formulation that consists of water, oil and amphiphile(s) which constitute a single optically isotropic and thermodynamically stable liquid solution (I. Danielsson and B Lindman, *Colloids Surf.* 3:391, (1981)). This provides a suitable amount of the local anaesthetic in the oil phase, which in turn confers a fast onset of action. No separate oil needs to be added to the composition, since the oil is already present by the active component(s) as such. A further advantage is that a thermodynamically stable composition is achieved in a temperature range of 5–40° C.

The pharmaceutical composition according to the present invention may advantageously also be used as a local anaesthetic on other surfaces and/or cavities than in the oral cavity. The composition may thus also be used vaginally, genitally and rectally.

The local anaesthetic(s) used for preparing a pharmaceutical composition according to the present invention may be selected from any local anaesthetic. Preferably the local anaesthetic as the starting material is in a non-ionized form.

In the final composition a fraction of the local anaesthetic or mixture of local anaesthetics are present in oil form. The size of this fraction, local anaesthetics in oil form, depends on the pH of the composition.

The best mode of performing the invention known at present, is to use the composition according to Example 1.

Methods of Preparation

The pharmaceutical composition according to the present invention may be prepared by the following steps:

(i) the local anaesthetic(s) and the surfactant with the lowest molecular weight if more than one surfactant is used, are melted together;

(ii) a part of the water is slowly added to the melt (i) during homogenization, forming an emulsion concentrate;

(iii) if more than one surfactant is used, the surfactant with the higher molecular weight is dispersed in water;

(iv) the emulsion concentrate of step (ii) and part of the surfactant solution of step (iii) are thoroughly mixed;

(v) the pH-value is adjusted by the addition of a suitable acid or base;

(vi) the weight is adjusted with water to the final weight of the composition.

The composition is preferably kept at 5° C. until a homogenous composition is obtained.

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

Example 1	[% by weight]
Lidocaine	2.50
Prilocaine	2.50
Lutrol F68 ®	5.50
Lutrol F127 ®	15.50
purified water up to a total weight of 100%.	

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 2	[% by weight]
Lidocaine	2.50
Prilocaine	2.50
Lutrol F68 ®	5.00
Lutrol F127 ®	16.25
purified water up to a total weight of 100%.	

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 3	[% by weight]
Lidocaine	2.25
Prilocaine	2.25
Lutrol F68 ®	3.5
Lutrol F127 ®	14.0
purified water up to a total weight of 100%.	

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 4	[% by weight]
Lidocaine	2.25
Prilocaine	2.25
Arlatone 289 ®	1.90
Adinol CT95 ®	0.07
Lutrol F127	14.00
purified water up to a total weight of 100%.	

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 5	[% by weight]
Lidocaine	2.25
Prilocaine	2.25
Arlatone 289 ®	1.90
Adinol CT95 ®	0.16
Lutrol F127	14.00
purified water up to a total weight of 100%.	

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

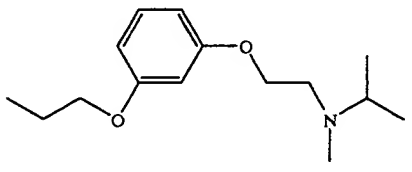
Example 6	[% by weight]
Lidocaine	2.25
Prilocaine	2.25
Arlatone 289 ®	1.90
Adinol CT95 ®	0.28
Lutrol F127	14.00
purified water up to a total weight of 100%.	

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

EXAMPLE 7 AND 8

In Examples 7 and 8, a local anaesthetic of the formula (I) was used as the acive ingredient.

(I)



This compound is disclosed in the International Patent Application PCT/SE96/01361.

The following pharmaceutical compositions were prepared.

Example 7	[% by weight]
Compound (I)	2.5
Lutrol F127 ®	17.0
Lutrol F68 ®	5.5
purified water up to a total weight of 100%.	

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 8	[% by weight]
Compound (I)	2.5
Lutrol F127 ®	20.0
Lutrol F68 ®	5.5
purified water up to a total weight of 100%.	

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

BIOLOGICAL STUDIES

A pharmaceutical composition according to Example 1 was applied to a human periodontal pocket with a blunt end needle. After an onset time of 30–45 seconds, a satisfactory anaesthetic effect had been achieved in order that periodontal scaling could be performed. The scaling was initiated, and the time taken to scale the tooth was noted. At the end of the scaling, the intensity of pain was measured by means of a visual analogue scale (VAS). The duration of the anaesthetic effect was 10–20 minutes.

We claim:

1. The pharmaceutical composition comprising:

(i) one or more local anaesthetics in oil form;

(ii) one or more surfactants in an amount effective to produce a homogenous formulation wherein, at least one surfactant has thermoreversible gelling properties; and

(iii) water;

wherein said composition is in the form of an emulsion or microemulsion and has thermoreversible gelling properties such that said composition is less viscous at room temperature than after introduction onto a mucous membrane of a patient.

2. The pharmaceutical composition according to claim 1, further comprising one or more taste masking agents.

3. The pharmaceutical composition according to claim 1, wherein said one or more local anaesthetics are present in an amount of 0.5–20% by weight based on the total weight of the composition.

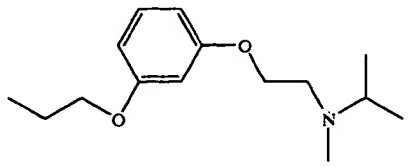
4. The pharmaceutical composition according to claim 3, wherein said one or more local anaesthetics are present in an amount of 2–7% by weight based on the total weight of the composition.

5. The pharmaceutical composition according to claim 1, wherein said one or more local anaesthetics is a eutectic mixture of local anaesthetics.

6. The pharmaceutical composition according to claim 5, wherein said one or more local anaesthetics is a eutectic mixture of lidocaine and prilocaine.

7. The pharmaceutical composition according to claim 1, wherein said one or more local anaesthetics comprises

(I)



8. The pharmaceutical composition according to any one of claims 1–7, comprising more than one surfactant of which at least one is a surfactant having thermoreversible gelling properties.

9. The pharmaceutical composition according to any one of claims 1–7, wherein the total amount of surfactant is present in an amount of up to 50% by weight based on the total weight of the composition.

10. The pharmaceutical composition according to any one of claims 1–7, wherein the surfactant is a non-ionic surfactant.

11. The pharmaceutical composition according to claim 10, wherein the surfactant is a poloxamer.

12. The pharmaceutical composition according to any one of claims 1–7, comprising the two surfactants Poloxamer 188® and Poloxamer 407®.

13. The method of treating a patient for pain associated with periodontal scaling, comprising applying to the periodontal pocket of said patient an effective amount of the pharmaceutical composition according to claim 1.

14. The process for the manufacture of the pharmaceutical composition according to claim 1, wherein said composition has more than one surfactant, comprising:

(a) melting together said one or more local anesthetics and the surfactant with the lowest molecular weight;

(b) adding water to the melt of step (a) during homogenization to form an emulsion concentrate;

(c) dispersing the remaining surfactant or surfactants in water;

(d) mixing, the emulsion concentrate of step (b) and the surfactant solution of step (c);

(e) adjusting the pH of the mixture of step (d) so that the final pH is greater than or equal to pK_a-1, wherein pK_a is that of the local anesthetic with the lowest pK_a; and

(f) adding water to the final weight of the composition.

15. A process for the manufacture of the pharmaceutical composition according to claim 1, wherein said composition has only one surfactant, comprising:

(a) melting together said one or more local anesthetics and said surfactant;

(b) addingc water to the melt of step (a) during homogenization to form an emulsion concentrate;

(c) adjusting the pH of the mixture of step (b) so that the final pH is greater than or equal to pK_a-1, wherein pK_a is that of the local anesthetic with the lowest pK_a; and

(d) adding water to the final weight of the composition.

16. The composition of claim 1, wherein said one or more local anesthetics comprise 0.5 to 20% of the final weight of said composition, and said one or more surfactants comprise up to 50% of the final weight of said composition.

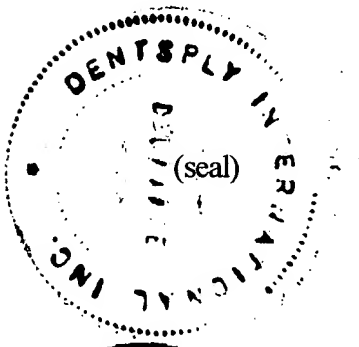
17. The composition of claim 16 wherein the pH of said composition is greater than or equal to pK_a-1, wherein pK_a is that of the local anesthetic with the lowest pK_a.

* * * * *

SECRETARY'S CERTIFICATE

I, Brian M. Addison, Vice President, Secretary and General Counsel, of DENTSPLY International Inc., do hereby certify that Maillefer Instruments Trading S.a.r.l., having an address at Chemin du Verger 3, CH-1338 Ballaigues, Switzerland, is an indirect wholly owned subsidiary of DENTSPLY International Inc., and that the name of the company was changed from Dentsply Anesthetics S.a.r.l. to Maillefer Instruments Trading S.a.r.l. effective January 1, 2001.

IN WITNESS WHEREOF, I have hereunto set my hand and the seal of the corporation DENTSPLY International Inc. this 13th day of February, 2004.



DENTSPLY INTERNATIONAL INC.

Secretary

Sworn to and subscribed before me this 13 day of February, 2004.

Notary Public

Notarial Seal
Nanette L. Porter, Notary Public
City of York, York County
My Commission Expires Aug. 20, 2005
Member, Pennsylvania Association of Notaries

EXHIBIT 7

United States Patent and Trademark Office

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Maintenance Fee Statement

6031007

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	6,031,007	1551	890	0	08/875,888	02/29/00	08/06/97	04	NO	PAID

909

ITEM NBR	ATTY DKT NUMBER
1	ABA300/13003

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Exhibit 8 Showing of patent claims, documenting manner claims read on Approved Product ORAQIX

Claim	Claim Limitation	ORAQIX Product Composition
Claim 1	The pharmaceutical composition comprising: (i) one or more local anaesthetics in oil form; (ii) one or more surfactants in an amount effective to produce a homogenous formulation wherein, at least one surfactant has thermoreversible gelling properties; and (iii) water; wherein said composition is in the form of an emulsion or microemulsion and has thermoreversible gelling properties such that said composition is less viscous at room temperature than after introduction onto a mucous membrane of a patient.	 See package insert, Exhibit 1: "lidocaine and prilocaine," "in oil phase" "Poloxamer excipients" having reversible temperature-dependant gelation "Purified water" "Gelation occurs at body temperature"
Claim 3	The pharmaceutical composition according to claim 1, wherein said one or more local anaesthetics are present in an amount of 0.5-20% by weight based on the total weight of the composition.	See Composition, Exhibit 4: 50 mg of lidocaine/prilocaine to 1000 mg is 5% of total weight of composition
Claim 4	The pharmaceutical composition according to claim 3, wherein said one or more local anaesthetics are present in an amount of 2-7% by weight based on the total weight of the composition.	See Composition, Exhibit 4: 50 mg of lidocaine/prilocaine to 1000 mg is 5% of total weight of composition
Claim 5	The pharmaceutical composition according to claim 1, wherein said one or more local anaesthetics is a eutectic mixture of local anaesthetics.	See package insert, Exhibit 1: which states a mixture of lidocaine and prilocaine is a "eutectic mixture."

Claim 6	The pharmaceutical composition according to claim 5, wherein said one or more local anaesthetics is a eutectic mixture of lidocaine and prilocaine.	See package insert, Exhibit 1: which states a mixture of lidocaine and prilocaine is a "eutectic mixture."
Claim 8	The pharmaceutical composition according to any one of claims 1-7, comprising more than one surfactant of which at least one is a surfactant having thermoreversible gelling properties.	See package insert, Exhibit 1: the gel contains thermosetting agents (Poloxamer 188 and Poloxamer 407) and said excipiants show reversible temperature dependant gelation.
Claim 9	The pharmaceutical composition according to any one of claims 1-7, wherein the total amount of surfactant is present in an amount of up to 50% by weight based on the total weight of the composition.	See Composition, Exhibit 4: 210 mg poloxamers in 1000 mg of composition is 21% by weight.
Claim 11	The pharmaceutical composition according to claim 10, wherein the surfactant is a poloxamer.	See Composition, Exhibit 4
Claim 12	The pharmaceutical composition according to any one of claims 1-7, comprising the two surfactants Poloxamer 188® and Poloxamer 407®.	See Composition, Exhibit 4
Claim 16	The composition of claim 1, wherein said one or more local anesthetics comprise 0.5 to 20% of the final weight of said composition, and said one or more surfactants comprise up to 50% of the final weight of said composition.	See Composition, Exhibit 4

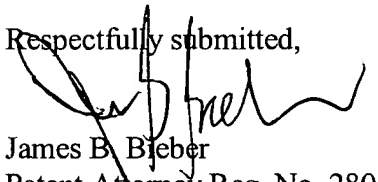
Exhibit 9 Relevant Dates for ORAQIX – IND and NDA

The IND application for ORAQIX was submitted on February 14, 1997, and the FDA acknowledged by letter receipt of the IND application on February 24, 1997, assigning IND number 52,677.

The NDA for ORAQIX was filed January 22, 2002. The NDA received an official receipt date of June 23, 2002 and was assigned NDA 21-451.

The NDA was approved by the FDA by an approval letter of December 19, 2003.

Respectfully submitted,



James B. Bieber
Patent Attorney Reg. No. 28054

February 13, 2004

Address of signer:

DENTSPLY INTERNATIONAL INC.
570 West College Avenue
York, PA 18405-0872
(717) 849-4514

Chronology
Oraqix
IND 52,677

EXHIBIT 10

Date		Event
01/31/97		FDA contact regarding filing strategy for Oraqix
02/06/97		FDA contact regarding FDA's determination of a new IND for Oraqix
02/14/97		Serial 000- Initial IND filed
02/24/97		FDA receipt letter for IND
03/04/97		FDA contact regarding request for additional copy of IND
03/04/97		Serial 001- Submission of desk copy of IND (see 3/4/97)
03/10/97		Serial 002- Submission of responses to FDA fax of 3/5/97
04/28/97		Serial 003- Reference to FDA's letter of 3/21/97 regarding dental consultants inquiries
05/13/97		Serial 004- Amendment #1 to protocol: a randomized double-blind placebo controlled to evaluate efficacy of dental gel for periodontal pocket anesthesia
05/16/97		Serial 005- Protocol amendment for addition of 10 clinical investigators for SP-DGA-0003 study
06/06/97		Record of Contact - new CSO at FDA, also requested samples of active and placebo
06/10/97		Record of contact - notification of sending of requested samples (see 6/6/97)
06/10/97		Serial 006- Submission of requested product and placebo product
07/22/97		Serial 007- Addition of Dr. Van Dyke to study SP-DGA-0003
04/10/98		Serial 008- Submission of final reports for SP-DGA-0001 and SP-DGA-0002
05/14/98		Serial 009- Request for meeting to discuss clinical development program
05/26/98		Record of contact - date proposed for meeting request
06/04/98		Record of contact - scheduled meeting for 8/26/98 for clinical study program
06/12/98		Record of contact - scheduled meeting 8/26/98
07/02/98		Serial 010 - Annual Report (2/20/97 - 3/31/98)
07/07/98		Serial 011- Change in ownership to Astra Pharmaceuticals
07/23/98		Record of Contact (Serial 011)
07/30/98		Serial 012 - Submission of new protocol SP-DGA-007, Investigator brochure, final report for SP-DGA-0003 and SP-DGA-0004
08/05/98		Serial 013 Response to FDA request for desk copies (serial 008,012)
08/10/98		Fax to FDA providing overheads for 8/26/98 meeting
08/11/98		Fax to FDA (retransmission of 8/10/98 fax)
08/14/98		Record of contact - discussion of serial #8,12
08/20/98		Fax to FDA - List of Astra Zeneca participants for 8/26/98 meeting
8/24 - 8/25/98		Record of contact - 8/27/98 clinical guidance meeting
09/10/98		Serial 015 - Amendment to protocol SP-DGA-0007 (serial 012) per FDA's recommendation regarding exclusion criterion
09/18/98		Minutes of 8/27/98 clinical guidance meeting
10/15/98		Record of contact - meeting minutes - 2,6 xylidine and carcinogenic risk
10/15/98		Record of contact - meeting minutes
10/29/98		Record of contact - notification of delay in NDA
10/29/98		Record of contact - regarding delay in NDA
11/18/98		Record of contact - clinical guidance meeting & 2,6 xylidine
01/12/98		Serial 016 - change in responsibility to New England Biomedical

07/19/99		Serial 017 - Annual Report (4/1/98 - 3/31/99)
08/13/99		FDA version of 8/27/98 meeting minutes
11/05/99		Submission (no serial #) - change in company name
12/07/99		FDA receipt of 11/5/99 submission
04/07/00		Serial 019 - change of address notification
04/24/00		FDA receipt letter- submission of serial 019
05/09/00		Serial 020 - Reauthorization of responsibilities
05/12/00		Serial 020 - CMC, Administrative change to protocol SP-DGA-007 and request for CMC meeting
06/26/00		Serial 021 - Annual Report (4/1/99 - 3/31/00)
08/09/00		Serial 022 - Addition of Dr. Magnusson for study SP-DGA-007
08/25/00		FDA Letter - Serial 021
08/31/00		Serial 023 - Addition of Dr. Geurs, study SP-DGA-0007
08/31/00		Serial 024 - Addition of CRO Omnicare
09/08/00		Serial 025 - Addition of Dr. Mariotti to study SP-DGA-0007
10/06/00		Serial 026 - Addition of Dr. Loomer to SP-DGA-0007 study
11/06/00		Serial 027 - Addition of co-investigators for Dr. Offenbacker and Dr. Mauriello
04/16/01		Serial 031 - Amendment to information package for 4/24/01 pre-NDA meeting
05/08/01		Serial 034 - Minutes of pre-NDA meeting - 4/24/01
07/12/01		Serial 035 - Annual Report (4/1/00 -3/31/01)
02/19/02		Serial 022 (036?) - Notification of DENTSPLY Pharmaceutical intent to file IND and authorization to reference Astra Zeneca's IND
06/03/02		Serial 023 - withdrawal of IND by Astra Zeneca

DA Chronology		
NDA 21-451		
Oraqix™		
Date		**Event**
11/21/01		Submission to FDA: Pediatric Waiver request
01/11/02		FDA letter Pediatric Waiver denial
01/22/02		Initial NDA submission (75 volumes) sent to FDA
01/23/02		Official receipt date of NDA by FDA
02/01/02		Letter to FDA providing the plan for responding to the Pediatric Wavier Denial
02/12/02		Record of contact between J. Grazal, AstraZeneca, Compliance Group and Debbie Pagano, FDA, Phila. District regarding FDA inquiries regarding addresses for manufacturer for NDA
02/15/02		Facsimile addressed to Ron Zentz from Kim Compton, FDA, providing copy of FDA receipt letter for NDA
02/18/02		Date of FDA letter (original) providing copy of FDA receipt letter
03/05/02		Record of contact between FDA and James Walker, Octagon Research, regarding electronic portion of NDA
03/07/02		Record of Contact (R. Zentz/ B. Manning) providing voice mail to Dr. Theordorakis (medical reviewer) regarding contact for questions
03/07/02		Facsimile to Kim Compton, FDA, from Bruce Manning, providing DENTSPLY Pharmaceutical representatives on teleconference of March 7, 2002
03/07/02		Facsimile from Kim Compton, FDA, providing FDA representatives on teleconference of March 7, 200
03/07/02		Record of contact between Dr. R. Zentz and Bruce Manning with Dr. Theodorakis, medical reviewer, regarding call to Lee Zagar and notification of new correspondent for NDA
03/07/02		Record of contact between Dr. Ron Zentz and Kim Compton, FDA, regarding correspondents to NDA and medical reviewer questions on NDA
03/07/02		Record of contact between Kim Compton, FDA, and Bruce Manning regarding electronic portion of NDA
03/08/02		Record of contact Bruce Manning and Kim Compton FDA regarding Tables 4 and 6 of ISS in NDA
03/08/02		Letter to FDA sending 3 desk copies Volume 1 NDA
03/10/02		Letter to FDA providing change in correspondent from Lee Zagar to Bruce Manning, consultant, and Karenlee Voltz, consultant, PAREXEL
03/12/02		Issuance of DENTSPLY Pharmaceutical (sponsor) version of minutes of teleconference of March 7, 2002
03/14/02		Record of contact between Kim Compton, FDA, and Bruce Manning regarding Tables to the ISS and scheduling of submission for 2/14/02 to respond to FDA's inquiries
03/14/02		Record of contact Bruce Manning and Kim Compton FDA regarding Tables 4 and 6 of ISS and medical reviewer needs.
03/14/02		Proof of Delivery of NDA Amendment to Oraqix NDA
03/14/02		Letter to FDA providing responses to requests as made in March 14, 2002, teleconference (Amendment to NDA)
03/15/02		Record of contact – Bruce Manning and FDA regarding delivery of Amendment to NDA
03/18/02		Letter to FDA providing a disk copy of the paper portion of the March 14, 2002, submission

03/22/02		E-mail from Kim Compton (FDA) to Bruce Manning regarding status of NDA and resolution of electronic submission (page 3 of teleconference minutes)
03/22/02		E-mail from Bruce Manning to Kim Compton (FDA) regarding resolution of missing data set
03/26/02		E-mail from Bruce Manning to Kim Compton (FDA) providing response to location of corrected data sets related to studies which use case report forms that had a checkbox "none" as an option for recording adverse events
03/27/02		E-mail from Kim Compton (FDA) to Bruce Manning regarding response to medical officer's request for AEs
04/01/02		Letter to FDA providing additional information on plans to respond to FDA denial of Pediatric Waiver
04/17/02		Record of contact between R. Zentz and M.Theodorakis, CMC reviewer, FDA regarding the correspondent for the NDA and initial CMC questions
04/17/02		Record of contact Dr. Theodorakis (FDA) and Bruce Manning regarding an individual contact person for each manufacturing facility
04/18/02		Voice mail from Bruce Manning to Dr. Theodorakis (FDA) regarding above-mentioned item
04/19/02		Record of contact Kim Compton (FDA) and Bruce Manning regarding above-mentioned item
04/23/02		Fax to FDA (Dr. Theodorakis) from Bruce Manning regarding request for one contact person for each manufacturing facility
04/23/02		Record of contact Bruce Manning and Kim Compton (FDA) regarding discussion of request for 90-day conference
05/10/02		Record of contact Bruce Manning & Kim Compton (FDA) regarding FDA request for Oraqix™ finished product & administration needles
05/14/02		Record of contact Bruce Manning & Kim Compton (FDA) regarding FDA request for samples of placebo used in clinical studies
05/22/02		Record of contact Bruce Manning & Kim Compton (FDA) regarding FDA request for disk copy of Item 8 of NDA
05/31/02		Desk copy of item 8 of NDA submitted
05/31/02		E-mail to Kim Compton (FDA) from Bruce Manning advising of desk copy submission
06/19/02		Record of contact Kim Compton (FDA) and Bruce Manning re samples of product per FDA's request and PowerPoint of instruments
06/24/02		Fax to Dr. Theodorakis (FDA) regarding contact staff for manufacturing facilities
06/24/02		Amendment submitted formally submitting the above-mentioned fax to the NDA
06/27/02		Submission of placebo samples to the FDA
07/02/02		Record of Contact (B. Manning) and Dr. Theodorakis, FDA regarding information on EMLA NDA
07/16/02		Record of Contact FDA requesting safety update on Oraqix™
07/17/02		Amendment filed to FDA providing Safety Update Report
07/22/02		Letter from FDA to Astra Zeneca, Sweden advisory of GMP inspection, 8/29-30/02
7/22-24/02		Record of Contact with International compliance group, FDA and Astra Zeneca - Notification of PAI Inspection
07/24/02		Record of contact, B. Manning, Kim Compton regarding advisory committee occurrence and GCP and GMP inspections
08/16/02		Amendment to NDA providing responses to Dr. Theodorakis inquiry of August 8, 2002 for CMC questions
08/16/02		E-mail to Kim Compton (FDA) from Bruce Manning providing contacts for the period 8/17-9/10/02

08/16/02		Record of contact - FDA and AstraZeneca for FDA Inspection of AstraZeneca Sweden for Oraqix NDA PAI
08/21/02		~~Email from FDA (Kim Compton) requesting clarification on ISS data for medical reviewer~~
08/21/02		Email to FDA confirming receipt of 8/21/2002 submission
08/26/02		Email to FDA advising of NDA Amendment filing to be couriered to FDA for 8/27/2002 delivery
~~08/26/02~~		~~Email from FDA (Kim Compton) regarding delivery of NDA Amendment~~
08/29/02		Facsimile from FDA requesting Desk copies of CMC section of NDA - for audit of Nordic Synthesis, Pre-Aprroval inspection of 11/4-7/2002
08/30/02		Record of contact - K. Voltz and Linda Adams, FDA regarding 8/29/2002 request for desk copies of CMC
~~09/03/02~~		~~Fax to FDA (Linda Evans) in response to request for disk copy of CMC section of NDA~~
09/04/02		Fax to FDA, Kim Compton providing copies of correspondence from and to Linda Adams, FDA
09/18/02		Record of contact - Dr. Theodorakis, FDA and B. Manning regarding status of Dental Application described in NDA on pages 004-001-306.
09/20/02		Amendment to NDA providing responses to Dr. Theodorakis' request of 9/18/02.
09/27/02		Record of contact. Bruce Manning and Kim Compton regarding request for full color mock-ups of labeling to be submitted to the safety staff
10/10/02		Record of contact: K. Voltz/K. Compton regarding FDA Request for color mock of labeling
10/10/02		E-mail from Kim Compton to Bruce Manning requesting information on discrepancies in Adverse Event tables for ISS.
10/10/02		E-mail from B. Manning to K. Compton providing response to above-mentioned e-mail
~~10/15/02~~		~~Record of contact: K. Voltz/J. Geiffer, St. Louis, FDA on the Nordic Synthesis (CAMBREX)~~ inspection (11/5-8,2002)
10/15/02		Record of contact: B. Manning and J. Gieffer, FDA regarding the above mentioned topic
10/15/02		Amendment to NDA -- submission of color copies of product labeling
~~10/17/02~~		~~Record of contact - K. Compton and Bruce Manning requesting the pka values of lidocaine and~~ prilocaine.
10/17/02		Record of contact - B. Manning/K. Compton - pka values provided for lidocaine and prilocaine
10/17/02		Record of contact - Mr. Gieffer, inspector, St. Louis, MO and Bruce Manning regarding inspection (PAI) of cambrex.
10/17/02		Record of contact - B. Manning and Mr. Geiffer, inspector, St. Louis MO regarding PAI inspection of CAMBREX.
10/18/02		E-mail to FDA providing values of pKa for lidocaine and prilocaine
11/08/02		FDA Discipline Review Letter - CMC
~~11/08/02~~		~~E-mail from FDA requesting copies of CRF's~~
11/08/02		E-mail to FDA regarding FDA's request for CRF's
11/18/02		Letter to FDA providing support for "low-risk" of injection of Oraqix
11/18/02		Letter to FDA providing commitment for conduct of pre-clinical studies per 11/15/2002 teleconference
11/20/02		~~FDA issuance of approvable letter for NDA~~
11/21/02		Letter to FDA of notice of intent to amend application

12/20/02		Correspondence to NDA on request for comment on a proposal for safeguards to prevent inadvertent injection of Oraqix
01/22/03		Correspondence providing request for end-of-review meeting for NDA
01/23/03		E-mail to FDA providing cover letter for end-of-review meeting request
01/23/03		E-mail from FDA in response to 1/23/2003 e-mail
01/31/03		Fax from FDA providing initial assessment of 12/21/02 submission on safeguards to prevent inadvertent injection of Oraqix™
02/05/03		Letter from FDA (1/22/03 letter) providing date of meeting as 3/19/03.
02/12/03		Letter to FDA accompanying additional 15 copies (desk) of pre-meeting package
03/14/03		Record of contact - Bruce Manning/Kim Compton regarding discussion of format for March 19, 2003, End-of-Review Meeting
03/14/03		Request for Designation
03/18/03		Fax to Kim Compton from Bruce Manning providing "labeling concepts" for discussion at March 19, 2003, Meeting
03/19/03		FDA Meeting
03/19/03		FDA's version of Meeting Minutes
03/19/03		Record of contact regarding prototypes of Oraqix Dispenser
03/19/03		Conduct of Review- End of Meeting
03/24/03		Record of Contact: FDA - Mark Kramer to discuss our withdrawal of the request for designation for Oraqix Dispenser
03/25/03		Record of Contact: FDA - Mark Kramer regarding Class I status for dispenser
03/25/03		Record of Contact: FDA - Mark Kramer regarding additional research on Class 1 status for dispenser
03/26/03		Record of Contact: FDA - Mark Kramer regarding research findings for Class I status for dispenser; Kramer was unavailable; left voicemail message
03/26/03		Record of Contact: FDA regarding prototype safety collars, prototype blunt-tip applicators, and prototype dispenser
03/27/03		Withdrawal of Request for Designation
03/27/03		E-mail from FDA on updated Methods Validation package
03/27/03		E-mail from FDA on updated Methods Validation package
03/28/03		End of Review Meeting, Sponsor's Version of Meeting Minutes
03/31/03		Submission of Table of Contents for Oraqix Dispenser for NDA Amendment
03/31/03		Record of Contact - FDA regarding Device Documentation
04/01/03		FDA response to Request to Withdraw Request for Designation
04/02/03		Record of Contact - FDA regarding Methods Validation Package
04/14/03		Record of Contact - FDA K. Compton - Oraqix dispenser samples
04/14/03		E-mail to FDA regarding submission of Dispenser Prototype
04/14/03		Submission of Samples and Justification of Safety of Dispensers
04/14/03		Record of Contact - FDA K. Compton regarding Zentz cell phone as contact point
04/15/03		Update to 04/14/03 submission - revise page 3 of letter, include Xylocaine samples
04/30/03		Correspondence - Preclinical Protocol - Chromosomal aberrations
05/01/03		Record of Contact - FDA K. Compton - status of 03/31/03 proposal for contents of the device
05/02/03		Correspondence - Comments to the FDA version of 03/19/03 meeting minutes
05/19/03		Correspondence - FDA response to 03/31/03 submission regarding device - recommends supplying sterile needles and making the collar difficult to remove
05/20/03		Record of Contact - FDA K. Compton - faxed letter of 05/19/03 will be revised to include additional comments from Dental reviewers; in the absence of statement regarding satisfactory status of submission packets, DP may assume FDA agrees.

06/19/03		Submission of 3 Volume NDA Amendment per FDA Approvable Letter November 20, 2002
06/19/03		Desk copy Volume 1 of NDA Amendment sent for K. Compton FDA and Word version of Oraqix package insert
06/19/03		Filing of Field Copy of Volumes 1 and 2 of NDA Amendment to Philadelphia District
06/26/03		Letter from FDA acknowledging receipt of resubmission. FDA considers this to be a complete, class 2 response to their 09/20/02 action letter and advising the user fee goal date is 12/20/03.
07/16/03		Record of Contact - FDA - B. Manning contacted K. Compton regarding the initial status of the NDA Amendment as filed on 06/20/03
07/17/03		Record of Contact: FDA: K. Compton contacted R. Zentz with questions resulting from the FDA Team Meeting held that day. Compton requested that two more copies of the Amendment be submitted without the Package Insert. Compton asked if there were any more dispenser prototypes available. Zentz responded that most were being used by vendors and consultants. Compton advised that she would contact DENTSPLY if additional dispensers are needed. Zentz inquired as to whether the collar and other methods to prevent injection were acceptable to the FDA. Compton could make a definitive statement, but felt the consensus was that these were acceptable. Zentz advised that samples of the modified collar will be available next week and some will be sent to the FDA along with Oraqix cartridges. Compton stated that the Review Team would like to have a teleconference with DENTSPLY in the next month or so. Zentz reviewed the action steps discussed during the call.
7/203/03		Submission to FDA of 2 Desk Copies of NDA Amendment
07/24/03		Submission of cartridges and collars from modified injection mold
08/14/03		Record of Contact- FDA requestion teleconference to discuss packaging.
08/15/03		E-Mail to Kim Compton, FDA, providing conference call-in number for August 19, 2003
08/19/03		Teleconference with FDA, DENTSPLY Pharmaceutical and New England Biomedical regarding proposed revisions to the cartridge label.
08/26/03		Record of Contact with FDA: Basis for selection of 505b(1)
09/17/03		Amendment to NDA - Additional information pursuant to June 19, 2003 and August 19, 2003 commitments.
11/21/03		Amendment which contains a response from the November 12, 2003 teleconference including proposed labeling.
11/25/03		E-mail from Bruce Manning to FDA advising of holiday staff coverage.
11/25/03		E-mail from FDA providing list of attendees from November teleconference.
11/25/03		Record of Contact: FDA responding to 11/21/03 labeling submission.
12/08/03		E-mail from FDA providing agenda for 12/8 conference call.
12/10/03		Record of Contact: FDA and Bruce Manning regarding final activities on Oraqix.
12/11/03		Amendment to NDA to include revised stability report and product specification pursuant to 12/8/03 teleconference.
12/12/03		E-mail from Bruce Manning to FDA attaching 1) the cover letter of the December 12 amendment 2) the immediate container label 3) the blister label.
12/12/03		Confirmation e-mail from Kim Compton of Bruce Manning's e-mail.
12/12/03		Electronic Submission of Revised Spec and Stability Report to FDA
12/17/03		E-mail from Bruce Manning to FDA advising of contact numbers for FDA to send their new proposals for the package insert.
12/17/03		E-mail from Kim Compton to Bruce Manning advising of the meeting to discuss the package insert.
12/17/03		E-mail from FDA providing final comments on label and Phase IV commitments.

12/18/03		E-mail submission to FDA of safety update report.
12/18/03		E-mail response to FDA regarding labeling statements.
12/18/03		Record of Contact with FDA confirming two teleconferences on December 19, 2003 to discuss labeling.
12/19/03		E-mail transmission of reference pursuant to FDA inquiry by Dan Mellon on labeling.
12/19/03		Amendment to NDA: Submission of Phase IV Commitment
12/19/03		Approval Letter of Oraqix

Exhibit 11

Statement That The Patent Is Eligible For Extension and Length of Extension Claimed

Applicant is of the opinion that US Patent 6,031,007 is eligible for extension under 35 USC 156, because it satisfies all the requirements under 35 USC 156, including claiming the approved product. Applicant notes that the term of the patent has not expired before this Application for Extension has been submitted; that the patent term has never before been extended; that the Application for Extension is being submitted by the owner of record of the patent; that the product has been subject to a regulatory review period before its commercial marketing or use; and that the regulatory permission is the first permitted commercial and marketing for use of the provision of law under which such regulatory review period occurred.

Statement as to the Length of Extension Claimed and Calculation thereof under 35 USC 156

Applicant claims an extension of patent term of: 1040 days, calculated as follows:

- Allowed extension is the sum of (1) IND period and (2) NDA period

(1) IND Period = 1791 days (date of NDA filing – date of IND filing)

\- 1100 days (date of issue of patent – date of IND filing)

691 ÷ 2 = 345 days

and

(2) NDA Period = 695 days (date of NDA approval – date of NDA filing) = 695 days

Σ 1040 days

• IND effective filing date: February 24, 1997
NDA effective filing date: June 22, 2002
. NDA approved: December 19, 2003
Patent Issue Date: February 29, 2000

[patent term extension exhibits]

Respectfully submitted,

James B. Bieber
Patent Attorney Reg. No. 28054

February 16, 2004

Address of signer:

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[patent term extension exhibits]

02-19-04

official Patent Term DAC

PATENT
F-MAIL

CERTIFICATE OF MAILING

By "EXPRESS MAIL"- Label No. EU898557835US

Date of Mailing by EXPRESS MAIL February 17, 2004

The Request for Extension of Patent Term for PHAR-1550 was mailed by EXPRESS MAIL on February 17, 2004

James B. Bieber

DENTSPLY International Inc.
570 West College Avenue
York, PA 17405-0872

Physically delivered to the United States Post Office, York, Pennsylvania by: Wendy L. Gohn

I hereby certify that this paper or fee is being deposited with the United States postal Service "EXPRESS MAIL Post Office To Addressee" service, under 37 CFR 1.10, as modified by 68 Fed. Reg. 14332 (March 25k 2003) on the date indicated above and is addressed to Commissioner for Patents, U.S. Patent and Trademark Office, 2011 South Clark Place, **Mail Stop Patent Extensions**, Ms. Karin Forriter, Esq., Crystal Plaza Three, D09, Arlington, VA 22202.

Wendy L. Gohn

Wendy L. Gohn
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